

Applicant : LEUNG, Shawn Shui-on
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In the claims

1.-13. (Canceled)

14. (Withdrawn) A method of constructing a re-engineered, or FR-patched immunoglobulin according to claim 1, 2, 3, 4, 5, 6, 7, 8, and 9 that will reduce the percentage of amino acid sequences derived from the parent immunoglobulin.

15. (Withdrawn) A method of constructing a re-engineered, or FR-patched immunoglobulin according to claim 1, 2, 3, 4, 5, 6, 7, 8, and 9 that will reduce the immunogenicity of the re-engineered, or FR-patched immunoglobulin, when used in the intended species (for example human), compared to that of the parent immunoglobulin.

16.- 19. (Canceled)

20. (Withdrawn) A method for treating a subject with a cancer which over expresses CD22 comprising administering to the subject an effective amount of a re-engineered immunoglobulin of claim 16.

21. (Withdrawn) The method of claim 20, where the cancer is Non-Hodgkin's lymphoma or rheumatoid arthritis.

22. (Withdrawn) A method for treating a subject with a cancer which over expresses CD20 comprising administering to the subject an effective amount of a re-engineered immunoglobulin of claim 17.

23. (Withdrawn) The method of claim 22, where the cancer is Non-Hodgkin's lymphoma or rheumatoid arthritis.

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24. (Withdrawn) A method for treating a subject with a cancer which over expresses an antigen which causes the cancer comprising administering to the subject with an effective amount of a re-engineered immunoglobulin which is capable of binding to said antigen according to claim 1.

25. (New) A re-engineered, or framework (FR)-patched immunoglobulin containing a heavy or light or heavy and light chain variable region sequences from a parent antibody, in which at least one of the compartmentalized framework sequences, defined as FR1, FR2, FR3 and FR4 are replaced, or patched by the corresponding compartmentalized framework sequences from the heavy or light or heavy and light chain immunoglobulin variable region of a different species, respectively, wherein said re-engineered immunoglobulin comprises compartmentalized framework sequences derived from at least two different sources of different immunoglobulin chains, wherein said different immunoglobulin chains can be sourced from different immunoglobulins of the same species or from different immunoglobulins of different species, and such re-engineered immunoglobulin binds specifically to an antigen with affinity within 10-fold or within 3-fold of, that of the parent immunoglobulin with the proviso that not all the replaced FR1, FR2, FR3 and FR4 of the re-engineered immunoglobulin heavy chain are from the same framework of a single immunoglobulin heavy chain; whereas not all the replaced FR1, FR2, FR3 and FR4 of the re-engineered immunoglobulin light chain are from the same framework of a single immunoglobulin light chain.

26. (New) A re-engineered, or framework (FR)-patched immunoglobulin containing a heavy or light or heavy and light chain variable region sequences from a parent antibody, in which at least one of the compartmentalized framework sequences, defined as FR1, FR2 and FR3 are replaced, or

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patched by the corresponding compartmentalized framework sequences from the heavy or light or heavy and light chain immunoglobulin variable region of a different species, respectively, wherein said re-engineered immunoglobulin comprises compartmentalized framework sequences derived from at least two different sources of different immunoglobulin chains, wherein said different immunoglobulin chains can be sourced from different immunoglobulins of the same species or from different immunoglobulins of different species, and such re-engineered immunoglobulin binds specifically to an antigen with affinity within 10-fold or within 3-fold of, that of the parent immunoglobulin with the proviso that not all the replaced FR1, FR2 and FR3 of the re-engineered immunoglobulin heavy chain are from the same framework of a single immunoglobulin heavy chain; whereas not all the replaced FR1, FR2 and FR3 of the re-engineered immunoglobulin light chain are from the same framework of a single immunoglobulin light chain.

27. (New) A re-engineered, or FR-patched immunoglobulin according to claim 25 or 26, in which the particular FR chosen for patching or replacing each corresponding FR in the parent immunoglobulin:

- a. exhibits the highest degree of homology, or at least 60%, to the corresponding parent FR;
- b. exhibits identical sequence homology to the corresponding parent FR at the three amino acids immediately adjacent to the flanking CDR's; and
- a. contains identical amino acid to the corresponding parent FR at positions known to be close to, or have interactions with the CDR's/antigen binding site, as evaluated by computer modeling, crystal structure, published information, or prior experience.

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28. (New) A re-engineered, or FR-patched immunoglobulin according to claim 25 or 26, in which the particular FR chosen for patching or replacing each corresponding FR in the parent immunoglobulin:

- a. exhibits the highest degree of homology, or at least 60%, to the corresponding parent FR;
- b. exhibits identical sequence homology to the corresponding parent FR at the four amino acids immediately adjacent to the flanking CDR's; and
- c. contains identical amino acid to the corresponding parent FR at positions known to be close to, or have interactions with the CDR's/antigen binding site, as evaluated by computer modeling, crystal structure, published information, or prior experience.

29. (New) A re-engineered, or FR-patched immunoglobulin according to claim 25 or 26, in which the particular FR chosen for patching or replacing each corresponding FR in the parent immunoglobulin:

- a. exhibits the highest degree of homology, or at least 60%, to the corresponding parent FR;
- b. exhibits the highest degree of sequence homology to the corresponding parent FR, preferably identical, or contains conservatively similar amino acids at the three amino acids immediately adjacent to the flanking CDR's; and
- c. contains identical, or conservatively similar amino acids to the corresponding parent FR at positions known to be close to, or have interactions with the CDR's/antigen binding site, as evaluated by computer modeling, crystal structure, published information, or prior experience.

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30. (New) A re-engineered, or FR-patched immunoglobulin according to claim 25 or 26, in which the particular FR chosen for patching each corresponding FR in the parent immunoglobulin:

- a. exhibits the highest degree of homology, or at least 60%, to the corresponding parent FR;
- b. exhibits the highest degree of sequence homology to the corresponding parent FR, preferably identical, or contains conservatively similar amino acids at the four amino acids immediately adjacent to the flanking CDR's; and
- c. contains identical, or conservatively similar amino acids to the corresponding parent FR at positions known to be close to, or have interactions with the CDR's/antigen binding site, as evaluated by computer modeling, crystal structure, published information, or prior experience.

31. (New) A re-engineered, or FR-patched immunoglobulin according to claim 25, 26, 27, 28, 29 or 30 containing the heavy or light or heavy and light chain variable region sequences from a parent antibody, in which the particular FR chosen for patching each corresponding FR in the parent immunoglobulin comprises re-introduced amino acids from the parent immunoglobulin framework outside the Kabat and Chothia CDRs, wherein the re-introduced amino acids replace corresponding amino acids in the patching FR, wherein the patching FR is the FR derived from a different source used for patching, or that replaces the original FR of, the parent immunoglobulin, and each of said re-introduced amino acids:

- a. is adjacent to a CDR in the donor immunoglobulin sequence, or

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- b. contains an atom within a distance of 4 Å of a CDR in said re-engineered immunoglobulin.

32. (New) A re-engineered, or FR-patched immunoglobulin according to claim 25, 26, 27, 28, 29 or 30 containing the light or heavy or heavy and light chain variable region sequences from a parent antibody, in which the particular FR chosen for patching each corresponding FR in the parent immunoglobulin comprises re-introduced amino acids from the parent immunoglobulin framework outside the Kabat and Chothia CDRs, wherein the re-introduced amino acids replace corresponding amino acids in the patching FR, wherein the patching FR is the FR derived from a different source used for patching, or that replaces the original FR of, the parent immunoglobulin, and each of said re-introduced amino acids:

- a. is adjacent to a CDR in the donor immunoglobulin sequence, or
- b. contains an atom within a distance of 5 Å of a CDR in said re-engineered immunoglobulin.

33. (New) A re-engineered, or FR-patched immunoglobulin according to claim 25, 26, 27, 28, 29 or 30 containing the heavy or light or heavy and light chain variable region sequences from a parent antibody, in which the particular FR chosen for patching each corresponding FR in the parent immunoglobulin comprises re-introduced amino acids from the parent immunoglobulin framework outside the Kabat and Chothia CDRs, wherein the re-introduced amino acids replace corresponding amino acids in the patching FR, wherein the patching FR is the FR derived from a different source used for patching, or that replaces the original FR of, the parent immunoglobulin, and each of said re-introduced amino acids:

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- a. is adjacent to a CDR in the donor immunoglobulin sequence, or
- b. contains an atom within a distance of 6 Å of a CDR in said re-engineered immunoglobulin.

34. (New) A re-engineered, or FR-patched immunoglobulin according to claim 25, 26, 27, 28, 29 or 30 containing the heavy or light or heavy and light chain variable region sequences from a parent antibody, in which the particular FR chosen for patching each corresponding FR in the parent immunoglobulin comprises re-introduced amino acids from the parent immunoglobulin framework outside the Kabat and Chothia CDRs, wherein the re-introduced amino acids replace corresponding amino acids in the patching FR, wherein the patching FR is the FR derived from a different source used for patching, or that replaces the original FR of, the parent immunoglobulin, and each of said re-introduced amino acids:

- a. is adjacent to a CDR in the donor immunoglobulin sequence, or
- b. is capable of interacting with amino acids in the CDRs, or
- c. is typical at its position for the species of the particular FR chosen for the patching, and the replaced amino acid in the said FR is rare at its position for the species from where the FR is derived.

35. (New) A re-engineered, or FR-patched immunoglobulin according to claim 25, 26, 27, 28, 29, 30, 31, 32, 33 or 34, which specifically binds to an antigen with an affinity of between 10^7 M^{-1} and 10^{11} M^{-1} .

36. (New) A re-engineered, or FR-patched immunoglobulin according to claim 25, 26, 27, 28, 29, 30, 31, 32, 33 or 34,

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which specifically binds to an antigen with an affinity of between 10^8 M^{-1} and 10^{10} M^{-1} .

37. (New) A re-engineered, or FR-patched immunoglobulin according to claim 25, 26, 27, 28, 29, 30, 31, 32, 33 or 34, which is substantially pure.

38. (New) A pharmaceutical composition comprising a re-engineered, or FR-patched immunoglobulin according to claim 25, 26, 27, 28, 29, 30, 31, 32, 33 or 34 in a pharmaceutically acceptable carrier.

39. (New) A re-engineered, or FR-patched immunoglobulin according to claim 25, 26, 27, 28, 29, 30, 31, 32, 33 or 34, wherein the re-engineered immunoglobulin binds specifically to an antigen with affinity within ten-fold of that of the parent immunoglobulin.